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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,381	03/24/2006	Jun Tomono	TOMONO 5	9348

1444 7590 01/29/2009

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
01/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,381	TOMONO ET AL.	
	Examiner	Art Unit	
	DELIA M. RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 7, 14-15 are pending.

Applicant's amendment of claims 7, 14-15, cancellation of claims 1-6, 8-13, 16-17, and amendments to the specification as submitted in a communication filed on 10/29/2008 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112, Second Paragraph

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 7, 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

3. Claim 7 (claims 14 and 15 dependent thereon) is indefinite in the recitation of "wherein degradation products of dsRNA with said polypeptide function in RNA interference as an siRNA" for the following reasons. As written it appears that the degradation products of double stranded RNA have a polypeptide function, which is unclear and confusing because RNA is not a polypeptide. For examination purposes no patentable weight will be given to the term. If Applicant's intended meaning is "wherein said polypeptide having RNase III activity cleaves double stranded RNA (dsRNA) in fragments which are used in RNA interference as short interfering RNA (siRNA)", the claim should be amended accordingly so long as support for that amendment can be found in the specification. Correction is required.

4. Claims 14 and 15 are indefinite in the recitation of "polypeptide having an RNase III activity which is defined by claim 7" for the following reasons. As written, it is unclear if the term "which is defined by claim 7" refers to the polypeptide of claim 7, the RNase III activity defined in claim 7, or both.

For examination purposes, it will be assumed that the claims read "which contains the polypeptide of claim 7". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

5. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

6. Claims 7, 14 and 15 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in the Non Final action mailed on 7/29/2008. It is maintained for the reasons of record and those set forth below.

7. Applicant argues that it is well known in the art that a polypeptide having at least 95% sequence identity to the polypeptide of SEQ ID NO: 4 or a polypeptide encoded by a nucleic acid which hybridizes under the conditions recited in claim 7 to the polynucleotide of SEQ ID NO: 1 has the same characteristics as those of the polypeptide of SEQ ID NO: 4 with a high probability. According to Applicant, it would be quite exceptional to have a variant of a protein where one amino acid residue has been substituted or a variant having 95% sequence identity to the protein with a different activity. Applicant also argues that a person of ordinary skill in the art can readily confirm that a particular polypeptide is not included in the claimed genus of polypeptides by testing for RNase III activity as taught in the specification. Furthermore, Applicant argues that since there are many patents which have been granted under similar situations, a precedent has been set and it is art accepted.

8. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner will not comment on the language used in the claims of other issued US

patents as each patent application is examined on its own merits and any discussion regarding the prosecution history of other patent applications would be improper herein. The Examiner acknowledges Applicant's amendments. However, the Examiner disagrees with Applicant's contention that the entire genus of polypeptides as claimed is adequately described.

Claim 7 has been amended to require polypeptides that are encoded by nucleic acids which hybridize to the polynucleotide of SEQ ID NO: 1 at a temperature of T_m- 25 °C overnight in a solution containing 6xSSC, 0.5% SDS, 5xDenhart's solution, and 100 µg/mL salmon sperm DNA.

Applicant states on the Remarks section of the response filed on 10/29/2008 that under the conditions recited the hybridization temperature is 71.89 °C and provides an equation for the calculation of T_m as described by Sambrook et al. where the value used for [Na+] is 0.99, the second term of the equation has been indicated as -16.6(log10[Na+]), and where the last term of the equation has been indicated as "600/l". Upon further review of this formula, it is noted that (1) the last term of the formula of Meinkoth and Wahl (same as that indicated in Sambrook et al.) is "500/l", (2) the second term is +16.6xlog10[Na+], and (3) the [Na+] value that should be used for the recited conditions, i.e., 6xSSC, should be 1.17 instead of 0.99 since 1xSSC contains 0.15 M NaCl and 0.15 M trisodium citrate at pH=7.0 (sodium citrate is a trisodium salt). The total [Na+] concentration in 6xSSC is 6x(0.15 + 3x0.015) = 1.17. See Ausubel, F., (Current Protocols in Molecular Biology, Hybridization Analysis of DNA Blots, pages 2.10.8-2.10.11, 1993) submitted with this Office action (page 2.10.8 for Meinkoth and Wahl equation and page 2.10.11 Table 2.10.3 for SSC composition). Using Applicant's estimation of the G+C content and l=678, T_m = 81.5 °C +16.6x$\log_{10}$[Na+=1.17] +0.41x(%GC=267*100/678) - .61x(%form=0) – 500/678 or T_m = 98.04 °C. Thus, T_m – 25 °C appears to be 73.04 °C and not 71.89 °C as asserted.

As known in the art, T_m is reduced by approximately 1 °C for each 1% mismatching, therefore under the conditions recited (6xSSC and 73.04 °C), one would expect at least 25% mismatching between the polynucleotide of SEQ ID NO: 1 and the target polynucleotide. It should be noted that the claims do

not recite any washing step, which as known in the art and taught by Ausubel, is the step which determines specificity in a hybridization reaction as specificity is a function of the temperature at which the washing step is carried out and the ionic strength of the final wash solution (page 2.10.10, right column, second full paragraph). Since the recited conditions are hybridization incubation conditions that promote base-pairing but are not intended to determine the specificity of the hybridization experiment, one would expect nonspecific binding and possibly hybridization with nucleic acids which have slightly more than 25% mismatching with respect to the polynucleotide of SEQ ID NO: 1. Assuming that the level of mismatching is 25%, the recited conditions allow for a genus of proteins which are encoded by nucleic acids which have 170 mismatches with respect to the polynucleotide of SEQ ID NO: 1 (170 = 0.25x678; SEQ ID NO: 1 = 678 nucleotides). Thus, the genus of polynucleotides recited can potentially encompass polynucleotides encoding proteins which are 25% sequence identical to the polypeptide of SEQ ID NO: 4 since the 170 mismatches can potentially alter 170 codons (25% = 100% -170x100/226; SEQ ID NO: 4 = 226 amino acids). The specification is silent with regard to which are the structural features required in any polypeptide having 25% sequence identity to the polypeptide of SEQ ID NO: 4 such that it displays the same RNase III activity as that of the polypeptide of SEQ ID NO: 4, nor does it teach a structure/function correlation which would allow one of skill in the art to determine a priori which are the structural variants within the genus of polypeptides recited which have the desired activity. Nothing is known with regard to the structural features present in the polypeptide of SEQ ID NO: 4 which are associated with the formation of dsRNA fragments of a particular size not present in other RNase III polypeptides. In the absence of an art-recognized structure/function correlation, it is unpredictable as to which structural variants of the polypeptide of SEQ ID NO: 4 will retain the same activity as that of the polypeptide of SEQ ID NO: 4 or how structural modifications to the polypeptide of SEQ ID NO: 4 will affect function. Therefore, for the reasons set forth above and those of record, one

cannot reasonably conclude that the claimed genus of polypeptides is adequately described by the teachings of the specification and/or the prior art.

9. Claims 7, 14 and 15 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 4, compositions and kits comprising said polypeptide, does not reasonably provide enablement for variants of the polypeptide of SEQ ID NO: 4 having RNase III activity, compositions and kits comprising said variants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in the Non Final action mailed on 7/29/2008. It is maintained for the reasons of record and those set forth below.

10. Applicant's arguments regarding the enablement rejection are those already summarized above.

11. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. It is reiterated herein that the Examiner acknowledges the amendments made to the claims as well as the teachings of the specification and the prior art. However, the Examiner disagrees with Applicant's contention that the entire scope of the claims is enabled by the teachings of the specification. It is noted that contrary to Applicant's assertion, one of skill in the art would not reasonably conclude that any variant of protein X having 95% sequence identity to protein X would have the same function as that of protein X. Similarly, one of skill in the art would not reasonably conclude that any protein encoded by a nucleic acid which hybridize under the incubation conditions recited in the claim to a polynucleotide which encodes protein X will have the same activity as protein X. The art as previously indicated teaches the unpredictability of determining a priori how the function of a protein will be affected by structural modifications without any guidance as to how structure correlates with a particular function. While it is agreed that there are instances where minor structural changes do not

significantly affect function, one of skill in the art would not accept that minor structural changes do not affect function as a generalization. The Examiner provided examples of how in some cases minor conservative substitutions can lead to unexpected changes in function. The art provides many examples of proteins which were first annotated as having a particular function based on structural homology and were later found to have a different activity when functionally characterized. Therefore, it is clear from the teachings of the art that structural homology does not necessarily translate into functional homology as suggested by Applicant. In the instant case, the structure/function correlation is required in view of the fact that according to the specification the RNase III activity of the polypeptide of SEQ ID NO: 4 is different from the RNase III activity of other polypeptides known in the art in that it degrades dsRNA in fragments of a particular size. The identity of those structural features required in any polypeptide having RNase III such that it can degrade dsRNA in fragments of a particular size is unknown. Thus, it is unclear as to how one of skill in the art can reasonably conclude that any of the structural variants of the polypeptide of SEQ ID NO: 4 recited in the claims is expected to have that particular RNase III activity, or how one could select a priori those structural variants of the polypeptide of SEQ ID NO: 4 which meet the structural limitations recited and also have the same RNase III activity as that of the polypeptide of SEQ ID NO: 4.

As stated above, the genus of polypeptides claimed can potentially encompass proteins having as little as 25% sequence identity to the polypeptide of SEQ ID NO: 4. Even if one were to assume that the mismatches only affect one third of the codons, thus encompassing proteins having 75% sequence identity to the polypeptide of SEQ ID NO: 4, in the absence of any knowledge or guidance as to which structural modifications can be made to the polypeptide of SEQ ID NO: 4 and maintain the desired RNase III activity, one of skill in the art would have to test an essentially infinite number of species to determine which ones display the recited activity.

The total number of variants of a polypeptide having a specific sequence identity can be calculated from the formula $N!x19^{A}/(N-A)!/A!$, where N is the length in amino acids of the reference polypeptide and A is the number of allowed substitutions for a specific % identity. Thus, for a variant of the polypeptide of SEQ ID NO: 4 having, for example, 75% sequence identity to SEQ ID NO: 4, the total number of variants to be tested is $226!x19^{57}/(226-57)!/57!$ (SEQ ID NO: 4 has 226 amino acids; 57 amino acids = 0.25x226) or $1.27x10^{127}$ variants. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Claim Rejections - 35 USC § 102

12. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

13. Claims 7 and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by Heidelberg et al. (protein disclosed in GenBank accession number AAN54413, October 23, 2002; DNA disclosed in GenBank accession number AE015579, December 2, 2002). This rejection has been discussed at length in the Non Final action mailed on 7/29/2008. It is maintained for the reasons of record and those set forth below.

14. Applicant argues that the polypeptide of Heidelberg et al. do not meet the 95% sequence identity limitation and asserts that the polynucleotide of SEQ ID NO: 1 would not hybridize under the conditions recited. Furthermore, Applicant argues that Heidelberg et al. do not teach the additional functional limitation recited in claim 7 regarding degradation products to be used as siRNA.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. As indicated above, the claims still encompass proteins having RNase III activity wherein said proteins have at least 25% sequence identity to the polypeptide of SEQ ID NO: 4. See extensive discussion of the scope of the claims in Claim Rejections under 112, first paragraph. See also Claim Rejections under 35 USC 112, second paragraph for claim interpretation and reasons why no patentable weight has been given to the additional functional limitation. Since Heidelberg et al. teach an RNase III isolated from *Shewanella oneidensis* MR-1 which is 85.4% sequence identical to the polypeptide of SEQ ID NO: 4 (85.4% = 193x100/226; 193 matches) and the polynucleotide encoding said polypeptide is 75.7% sequence identical to the polynucleotide of SEQ ID NO: 1, it is expected to hybridize under the incubation conditions recited. See extensive discussion above regarding the amount of mismatching allowed by the conditions recited. Therefore, the teachings of Heidelberg et al. anticipate the instant claims as written/interpreted.

16. Claim 15 was rejected under 35 U.S.C. 102(b) as being anticipated by Trotta et al. (Cancer Cell 3(2):145-160, February 2003). This rejection has been discussed at length in the Non Final action mailed on 7/29/2008.

17. In view of the fact that the *E. coli* RNase III disclosed in the prior art is 66.8% sequence identical to the polypeptide of SEQ ID NO: 4 (66.8% = 151x100/226) and its polynucleotide is not 75% or more sequence identical to the polynucleotide of SEQ ID NO: 1, this rejection is hereby withdrawn.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill

in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a). This rejection is necessitated by amendment.

20. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Heidelberg et al. (protein disclosed in GenBank accession number AAN54413, October 23, 2002; DNA disclosed in GenBank accession number AE015579, December 2, 2002). This rejection is necessitated by amendment.

The teachings of Heidelberg et al. have been discussed in the previous Office action and reiterated above. Heidelberg et al. do not teach a kit comprising the RNase III polypeptide.

Claim 15 is directed to a kit for degrading dsRNA comprising the polypeptide of claim 7. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a kit comprising dsRNA substrate and the polypeptide of Heidelberg et al. A person of ordinary skill in the art is motivated to make such kit because Heidelberg et al. teach that their polypeptide is an RNase III and one of skill in the art would have been interested in further characterizing the enzyme. Placing those reagents required to carry out an enzymatic assay in a kit would be desirable because it would save time to have all the required reagents together. One of ordinary skill in the art has a reasonable expectation of success at making the kit because all that is required is to gather the required components in a single package. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Allowable Subject Matter

21. The polypeptide of SEQ ID NO: 4 appears to be allowable over the prior art of record.

Conclusion

22. No claim is in condition for allowance.

23. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can

normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez
Primary Patent Examiner
Art Unit 1652

DR
January 29, 2009